Prospective isolation of human embryonic stem cell-derived cardiovascular progenitors that integrate into human fetal heart tissue.

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Authors: Reza Ardehali, Shah R Ali, Matthew A Inlay, Oscar J Abilez, Michael Q Chen, Timothy A Blauwkamp, Masayuki Yazawa, Yongquan Gong, Roeland Nusse, Micha Drukker, Irving L Weissman

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Public Summary:
Heart disease remains the leading cause of morbidity and mortality in the western world, however, therapies for end-stage heart failure are limited. The goal of regenerative medicine is to use human embryonic stem cells (hESCs) as a source to produce cardiac cells for regeneration of the damaged heart muscle. In this article, we identified four surface markers (proteins that are expressed on the cell surface) that can be used prospectively to isolate stem cells that are committed to regenerate human hearts. These cells were shown to be able to generate heart muscle cells and the cells that make up the linings of blood vessel walls. We transplanted these cells into a mouse, and showed that they mature to heart muscle and blood cells but failed to incorporate functionally into the mouse hearts. This could be due to the inherent differences between a mouse and a human heart: for example, the average rate of contraction is 600 beats per minute for a mouse heart but 60 beats per minute for a human heart. Therefore, we sought to investigate whether these cells can functionally integrate into human hearts. Human fetal heart tissues (obtained for research purposes) were transplanted into the ear of a mouse, where the tissue remains viable. The cardiac stem cells derived from hESCs were then transplanted into these human fetal heart tissues and were shown to mature to heart muscle cells. In addition, these cells structurally and functionally incorporated into the human heart tissue. These studies help set the platform for future clinical application of stem cells to treat heart disease.

Scientific Abstract:
A goal of regenerative medicine is to identify cardiovascular progenitors from human ES cells (hESCs) that can functionally integrate into the human heart. Previous studies to evaluate the developmental potential of candidate hESC-derived progenitors have delivered these cells into murine and porcine cardiac tissue, with inconclusive evidence regarding the capacity of these human cells to physiologically engraft in xenotransplantation assays. Further, the potential of hESC-derived cardiovascular lineage cells to functionally couple to human myocardium remains untested and unknown. Here, we have prospectively identified a population of hESC-derived ROR2(+)/CD13(+)/KDR(+)/PDGFRalpha(+) cells that give rise to cardiomyocytes, endothelial cells, and vascular smooth muscle cells in vitro at a clonal level. We observed rare clusters of ROR2(+) cells and diffuse expression of KDR and PDGFRalpha in first-trimester human fetal hearts. We then developed an in vivo transplantation model by transplanting second-trimester human fetal heart tissues s.c. into the ear pinna of a SCID mouse. ROR2(+)/CD13(+)/KDR(+)/PDGFRalpha(+) cells were delivered into these functioning fetal heart tissues: in contrast to traditional murine heart models for cell transplantation, we show structural and functional integration of hESC-derived cardiovascular progenitors into human heart.

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